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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,458	08/04/2006	Susanne Matheus	MERCK-3217	5757

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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	PAPER NUMBER
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,458	MATHEUS ET AL.	
	Examiner	Art Unit	
	CLAIRE KAUFMAN	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *09 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,8,11 and 16-24* is/are pending in the application.

4a) Of the above claim(s) *18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,8,11,16,17 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,4,8,11 and 16-24* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/9/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 2, 3, 5-7, 9, 10 and 12-15 have been cancelled rendering rejection(s) of them mute.

The rejection of claims 1, 8, 12-17 and dependent claims 2-7 and 9-14 under 35 USC 112, second paragraph, is withdrawn in view of the amendment to or cancellation of the claims.

The rejection of claims 8-10 and 13-17 under 35 U.S.C. 102(b) as being anticipated by WO 03/007988 A1 is withdrawn in view of the amendment to or cancellation of the claims.

The rejection of claims 1-4, 8-11 and 15-17 under 35 U.S.C. 102(a) as being anticipated by US 2003/0138417 A1 is withdrawn in view of the amendment to or cancellation of the claims.

As amended, claim 16 is no longer rejected under 35 USC 103, since it depends from a cancelled claim and, therefore, its subject matter and scope cannot be determined. Similarly, new claim 21 will not be rejected under 35 USC 103 for the same reason.

New: ***Claim Rejections - 35 USC § 112, Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 (amended) and 21 (new) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16 and 21 recite the limitation "claim 7". There is insufficient antecedent basis for this limitation in the claims. Claim 7 has been cancelled.

Claim 21 is also indefinite because it recites “an additional medicament active ingredient”, however, it is unknown what the intended activity is. Therefore, the metes and bounds of the claim are not clear.

Double Patenting

Claims 1, 8 and 16-17 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13, 15-24 and 26-27 of copending Application No. 10/996,597 in view of US 6,171,586 ('586) for the reasons set forth in the previous Office action.

Applicants' intention of addressing this rejection once the instant claims are otherwise allowable is acknowledged.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 8, 11 and 17 remain and new claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sridhar et al. (Lancet Oncol., 4(7): 397-406, July 2003) and WO 02/096457 A2 for the reasons set forth in the previous Office action (repeated below) and for the following reason addressing new claims 22-24: The use of the term "consisting essentially of" in the new claims does not introduce a significant change to the subject matter compared to the claims previously rejected, such that the rejection is equally applicable to these new claims.

Sridhar et al. teaches (two paragraph beginning p. 398 col. 2 with the second full paragraph) that:

> Monoclonal antibodies have been developed that target different members of the EGFR superfamily. They are highly specific with few side-effects and may be synergistic with chemotherapy and radiation….
>
> Cetuximab (IMC-C225) is a human-murine chimeric IgG monoclonal antibody that competitively binds to the extracellular domain of EGFR.... Preclinical studies show that cetuximab inhibits the proliferation of cell lines expressing EGFR and increases the cytotoxic activity of chemotherapy and radiation. Cetuximab alone and in combination with chemotherapy or radiotherapy was generally well tolerated in phase I trials.... Cetuximab in combination with chemotherapy has shown activity in head and neck and colorectal cancers with acceptable toxic effects.

Sridhar et al. also discuss other EGFR antibodies in clinical trials as cancer therapies, including EMD72000 (Table 1 and p. 400, col. 1, first full paragraph). Sridhar et al. do not discuss antibody formula concentration or the means of concentrating an antibody formulation.

WO 02/096457 teaches highly concentrated formulations of antibodies with concentration of at least 50mg/ml up to 250 mg/ml and methods of making them by ultrafiltration (p. 4, first and second full paragraphs and, *e.g.*, p. 22, first full paragraph). The desirability of the antibody formulation is stated (p. 2, middle): "Thus, there is a demand on the market for stable, liquid, injectable antibody formulations; and, in particular, for highly concentrated stable liquid, injectable antibody formulations. There is also a need for stable aqueous solutions comprising a high concentration of antibody protein that can be used as a starting material or intermediate in process to obtain stable liquid antibody formulations of the invention." The advantage of highly concentrated formulations being suitable for pre-filled delivery devices because of the small volume needed is also discussed (p. 7, first full paragraph). Additionally taught is that the antibodies may be monoclonal, including chimeric antibodies which are humanized, antibody fragments and antibody derivatives which are PEGylated (p. 9, first full paragraph through p. 10, first full paragraph). Excipients for the formulations are disclosed (*e.g.*, middle of p. 13).

It would have been obvious to the artisan of ordinary skill at the time the invention was made to have cetuximab or other EGFR antibody in clinical trials (monoclonal and/or humanized, including EMD72000) as described by Sridhar et al. in a highly concentrated formulation because WO 02/096457 teach the demand on the market for one that can be

injectable and/or can serve as a starting material or intermediate to obtain a suitable therapeutic formulation. It would have been obvious to use ultrafiltration as a means of concentrating the antibody formulation because WO 02/096457 teaches that this part of a general method for preparation of high concentrated liquid formulations.

Applicants argue (middle of p. 8) that WO 02/096457 teaches IgE antibodies and does not teach or suggest "antibodies having specific epitopes". The reference is especially silent with respect to monoclonal antibodies. The argument has been fully considered, but is not persuasive. It is noted that antibodies are not referred to as having "epitopes", but the region of the antigen to which they bind is called an epitope. WO 02/096457 discusses monoclonal antibodies, such as E25 (p. 4, second full paragraph), which is indeed an IgE antibody (p. 8, second full paragraph). Monoclonal antibodies in general are discussed on p. 9. While the preferred embodiment is an anti-IgE antibody (p. 10, second full paragraph), there is no limitation on the type of antibody for which the concentrating process may be used. At the bottom of page 18 it is stated, "The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention." Example 7, for example, is entitled "General method for the preparation of high concentrated liquid formulations." It simply requires "a solution of purified antibody" and provides E25 as a non-limiting example. Further, claim 1 is drawn to a stable aqueous solution comprising an antibody at a concentration at least 50 mg/ml, without limitation on type of antibody. Claim 28 is an example of a process for the preparation of a therapeutic liquid formulation wherein the generic antibody is concentrated to more than 150 mg/ml. Because the advantages of highly concentrated therapeutic antibody formulations are taught, as well as in depth methods for their production, WO 02/096457 does provide the teaching and suggestion to highly concentrate in aqueous solution therapeutic antibodies, even though particular non-IgE antibodies are not listed.

Applicants argue (bottom of p. 8) that "Preparations of highly concentrated liquid formulations of antibodies are afflicted with technical challenges and routine protocols for protein concentration are not always applicable for large proteins with specific properties, such as, monoclonal antibodies." WO 02/096457 only discloses generic methods of concentrating proteins which are non-specific antibodies without specific epitopes. Sridhar et al. discloses

EGFR antibodies only at very low concentration. Therefore, the instant invention is not obvious over the prior art. The argument has been fully considered, but is not persuasive. WO 02/096457 does not disclose generic methods for non-specific antibodies. First, IgE antibodies have two antigen binding sites and are specific for different types of allergens, for example pollen *versus* milk protein. Second, WO 02/096457 discloses concentration methods for antibodies, including monoclonal antibodies. For the method, the particular specificity of the antibody is unimportant. The use of a prior art anti-EGFR antibody such as cetuximab in the method of WO 02/096457 where the exemplary antibody was an IgE antibody is a case in which the artisan of ordinary skill would have recognized the substitution of one known antibody for another yielding predictable results. WO 02/096457 provides the motivation for concentrating a therapeutically effective antibody (see rejection above): "The desirability of the antibody formulation is stated (p. 2, middle): "Thus, there is a demand on the market for stable, liquid, injectable antibody formulations; and, in particular, for highly concentrated stable liquid, injectable antibody formulations." The artisan of ordinary skill would have recognized the advantage of concentrating a therapeutically effective antibody and would have been motivated to use with a reasonable expectation of success the method of WO 02/096457.

Art of Record

Newly cited reference filed with the IDS of 12/09/08, Harris et al., Drug Dev. Res. 61:137-154, 2004, is not available as prior art, having been published March 2004.

WO 04/085474, also cited on the IDS of 12/09/08, is cumulative with the above references for a method of producing a concentrated liquid formulation comprising an EGFR antibody; however, no actual concentrations are provides (see especially [20] and [33]).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire Kaufman, Ph.D.
/Claire Kaufman/
Patent Examiner, Art Unit 1646
March 13, 2009

Lorraine Spector, Ph.D.
/Lorraine Spector/
Primary Examiner, Art Unit 1647